Training course:
All About Clinical Trials

How to interpret clinical trial data – Examples from clinical trials

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Declaration of Conflict of Interest

The existence of potential conflicts of interest does not necessarily indicate a bias. However it is our ethical obligation to inform organisers and participants so that they are made aware of any relationship that might cause unintentional bias. A potential conflict of interest may arise from various relationships, past or present, such as employment, consultancy, investments and stock ownerships, funding for research, family relationship etc.

☐ I have no potential conflict of interest to report

X I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	**Name of commercial company**
Receipt of grants/research supports:	No
Receipt of honoraria or consultation fees:	Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, Pfizer, Apontis
Participation in a company sponsored speaker's bureau:	Amgen, AstraZeneca, Berlin Chemie, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Merck Sharp Dohme, Novartis, Pfizer
Stock shareholder:	No
Spouse/partner:	No
Other support (please specify):	No

What do you have to know from the trial?

- WHY
- WHO
- HOW

WHY — Goals / Hypothesis

IMPROVE-IT

First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

- **Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?**
- **"Is (Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)**
- **Safety of ezetimibe**

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

WHO — Patient Population

Inclusion Criteria:

- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc,
    prior CABG > 3 years, multivessel CAD
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease

HOW — Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12

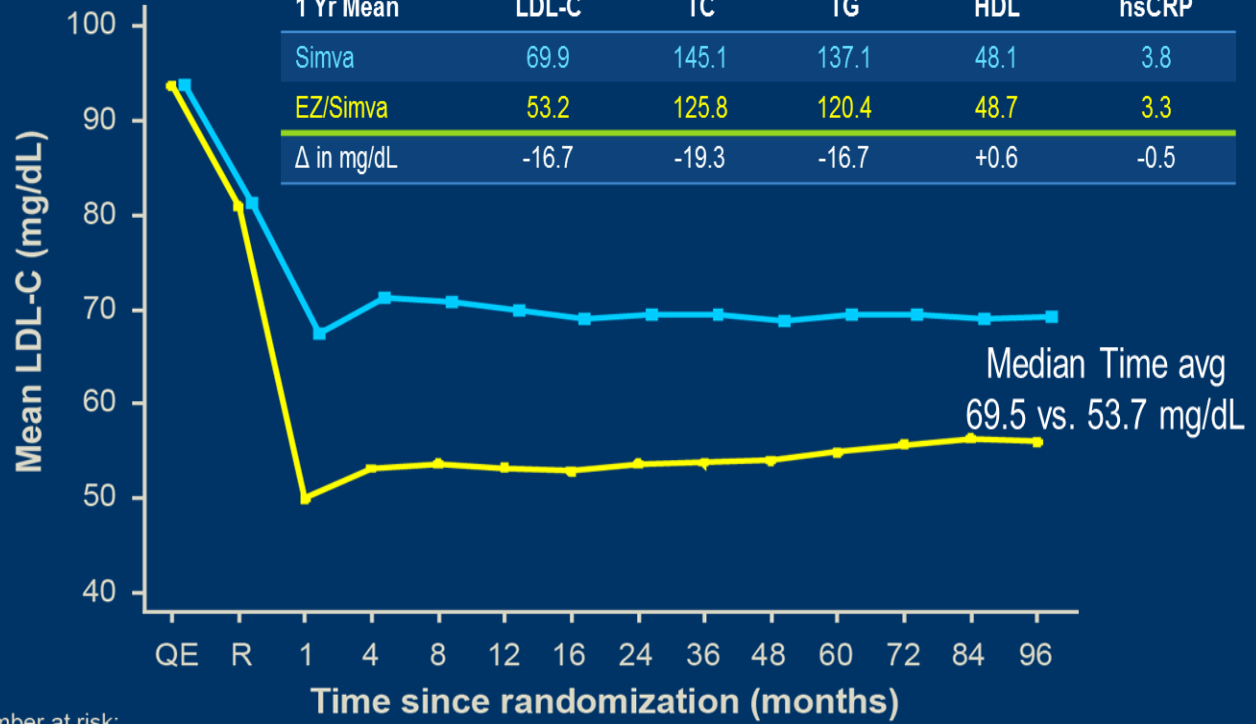
Baseline Characteristics

	Simvastatin (N=9077) %	EZ/Simva (N=9067) %
Age (years)	64	64
Female	24	25
Diabetes	27	27
MI prior to index ACS	21	21
STEMI / NSTEMI / UA	29 / 47 / 24	29 / 47 / 24
Days post ACS to rand (IQR)	5 (3, 8)	5 (3, 8)
Cath / PCI for ACS event	88 / 70	88 / 70
Prior lipid Rx	35	36
LDL-C at ACS event (mg/dL, IQR)	95 (79, 110)	95 (79,110)

Cannon et al., N Engl J Med 2015;372:2387-97

LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5



Number at risk:

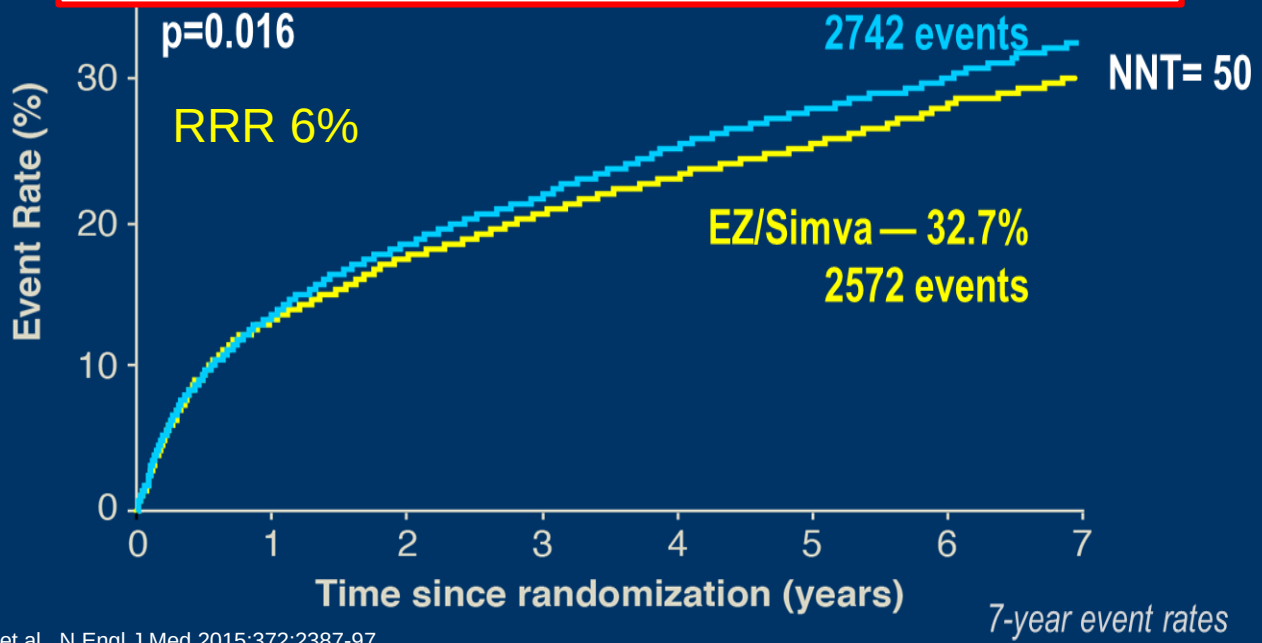
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

Cannon et al., N Engl J Med 2015;372:2387-97

Primary Endpoint — ITT

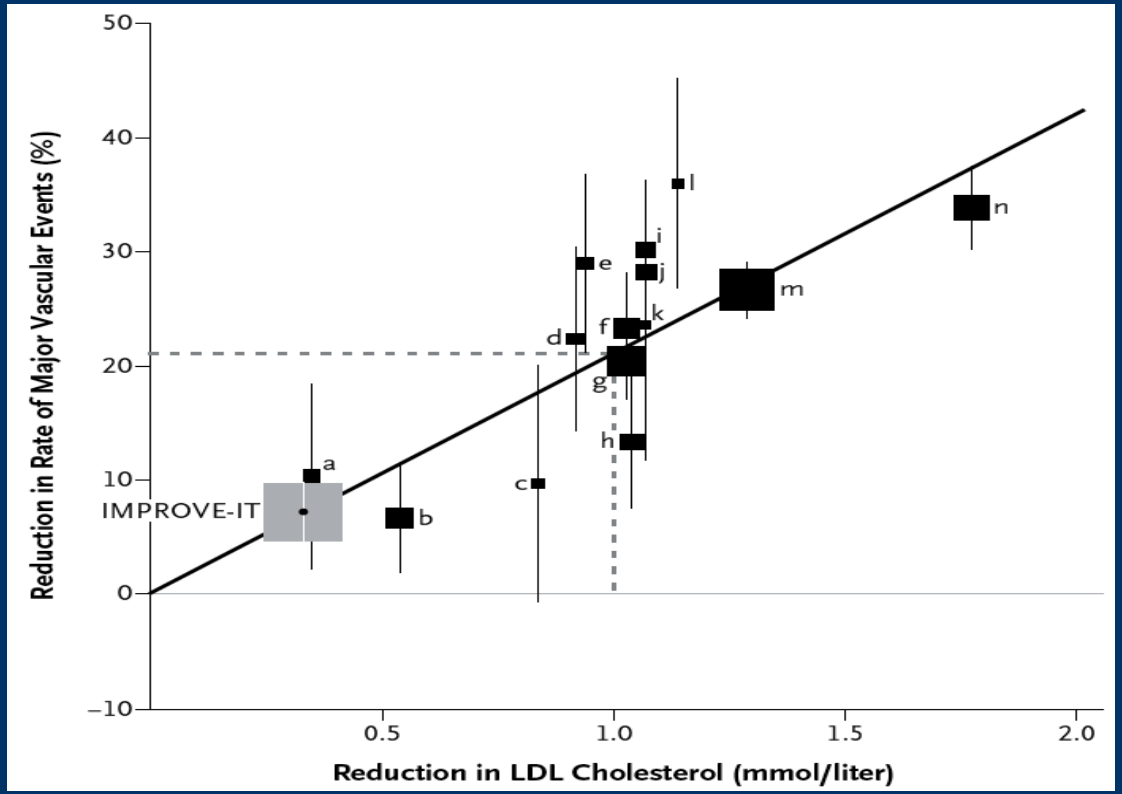
Cardiovascular death, MI, documented unstable angina requiring reho

What does this mean?



Cannon et al., N Engl J Med 2015;372:2387-97

Primary Endpoint — Interpretation



Cannon et al., N Engl J Med 2015;372:2387-97

Primary and 3 Prespecified Secondary Endpoints — ITT

Secondary endpoints valid?

Cannon et al., N Engl J Med 2015;372:2387-97

“Levels“ of Endpoints

Level 1 — **All-cause mortality**

Level 2 — **Cause-specific mortality** — fatal MI

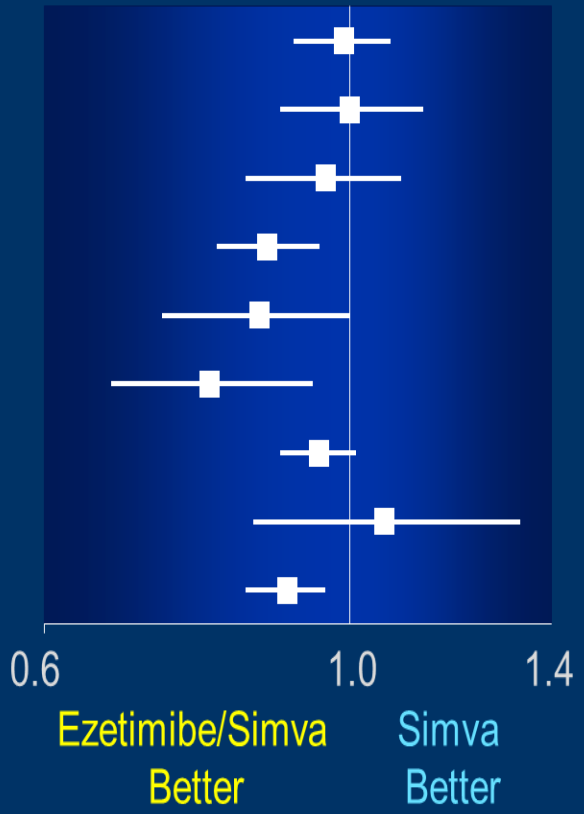
Level 3 — **Non-fatal clinical events** — a) Non-fatal MI; b) hospitalisation

Level 4 — **Surrogates** — e.g. LDL cholesterol

Level 5 — **Quality of life**

Lubsen J et al., Stat Med 2002; 21:2959-70

Individual Cardiovascular Endpoints and CVD/MI/Stroke



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002 *
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008 *
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003 *

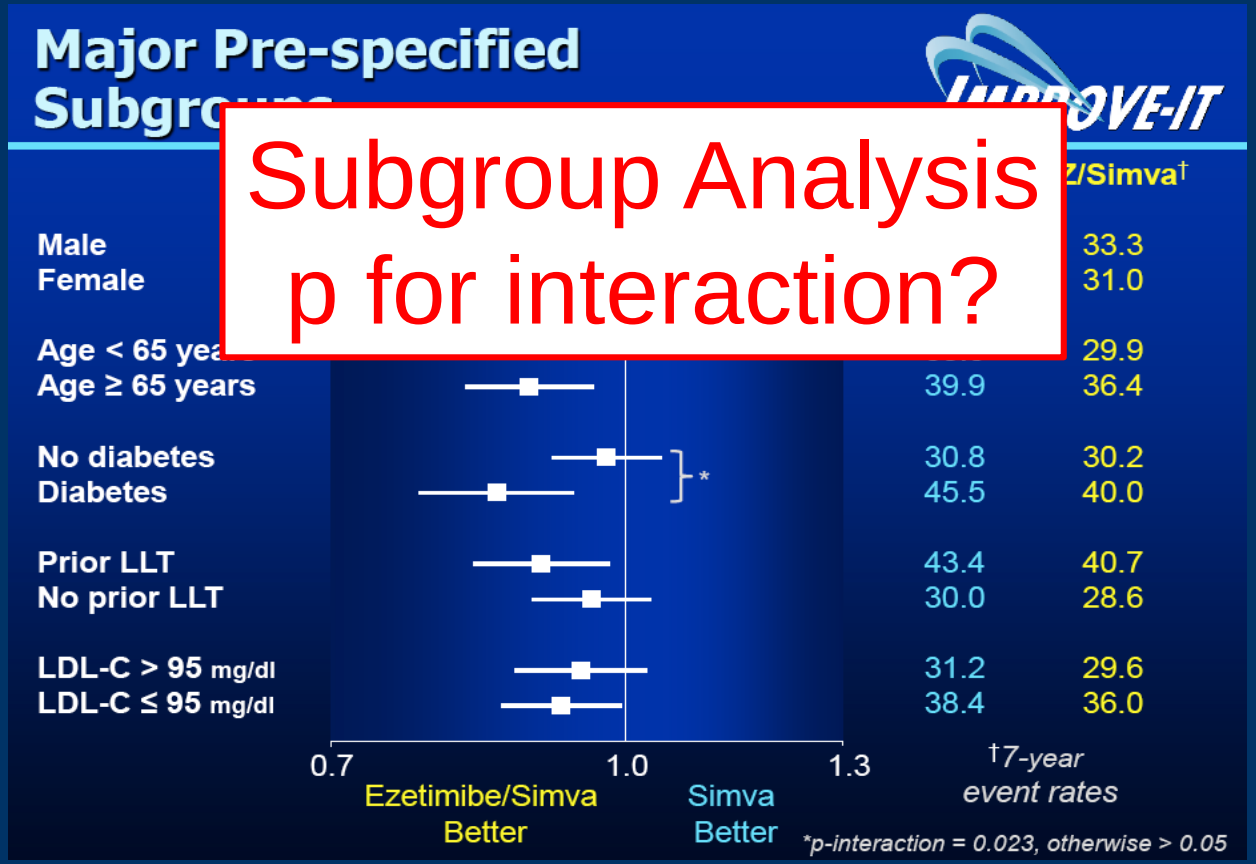
*7-year event rates (%)

Cannon et al., N Engl J Med 2015;372:2387-97

Validity of Subgroup Analysis - Rule of 4 P’s

- **P**respecified
- **P**owered
- **P**lausible
- **P**ractically relevant

Subgroup Analysis



Subgroup Analysis
p for interaction?

Cannon et al., N Engl J Med 2015;372:2387-97

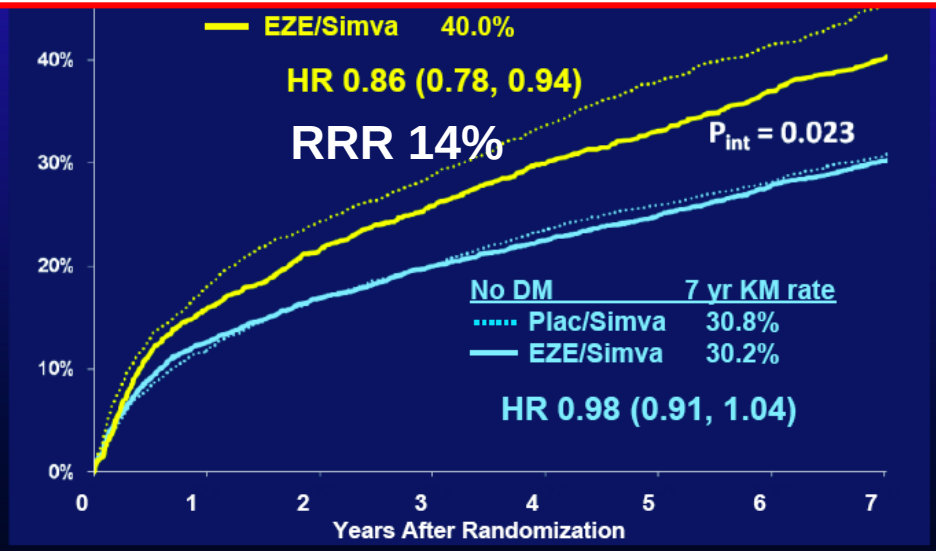
Subgroup Analysis

4.933 (27%) pts with Diabetes

Primary Endpoint — ITT

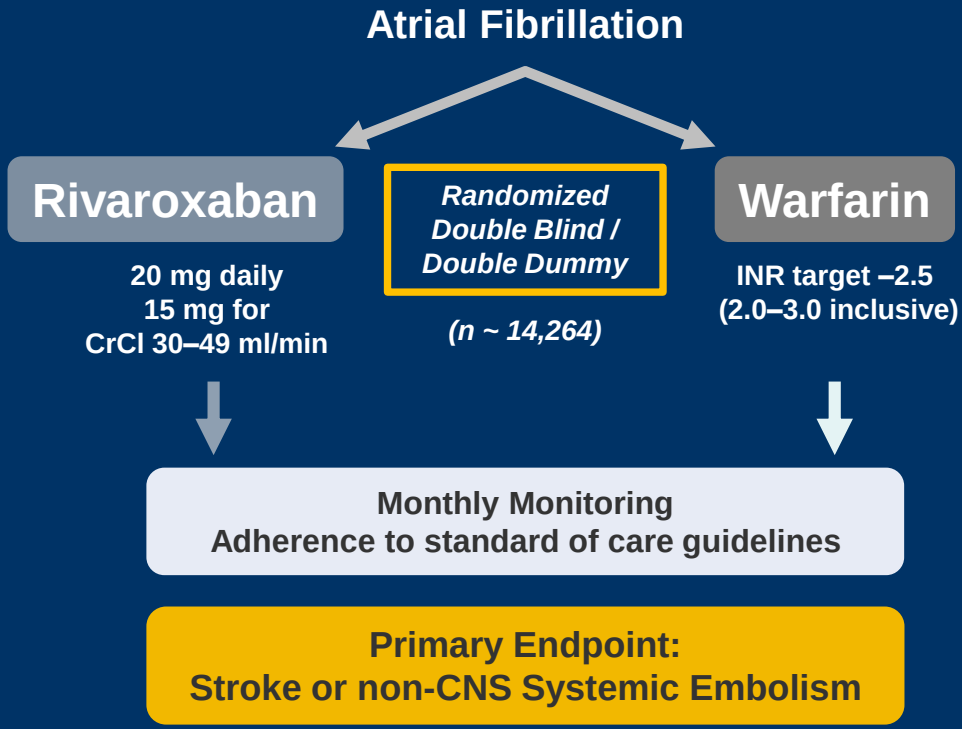
IMPROVE-IT

What does this mean?



Giugliano et al., Presentation at ESC 2015

Study Design



Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required *

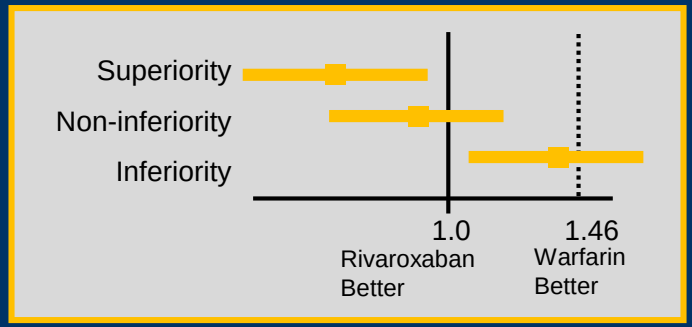
OR
- Stroke, TIA or Systemic embolus

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10 %

Mahaffey; Oral presentation at AHA, 15th November 2010
Patel MR et al. *N Eng J Med* 2011; 365: 883-991

Statistical Methodologies

- **Sample Size**
  - Warfarin event rate ~2.3
  - Type 1 error 0.05 (2-sided)
  - 405 events; > 95 % power
  - ~14,000 patients

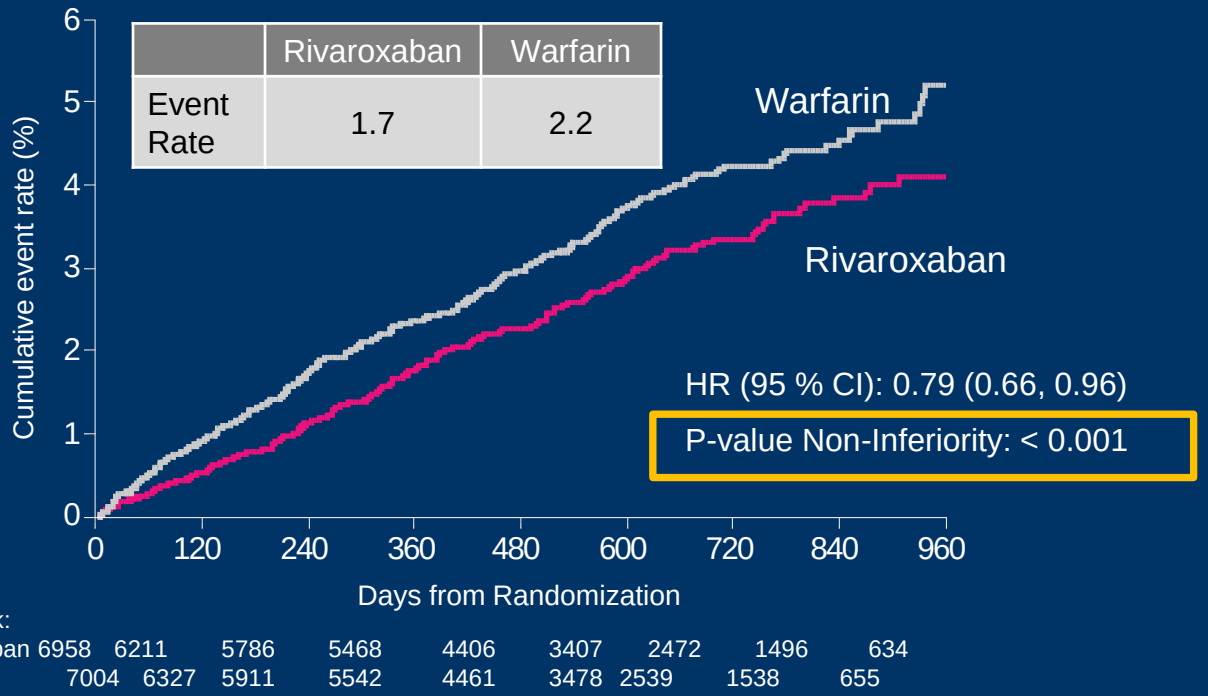


- **Primary Efficacy Evaluation:** Stroke or non-CNS Embolism
  - Non-Inferiority: Protocol compliant on treatment
  - Superiority: On Treatment and then by Intention-to-Treat

- **Primary Safety Evaluation:**
  Major or non-Major Clinically Relevant Bleeding

Mahaffey ; Oral presentation at AHA, 15th November 2010

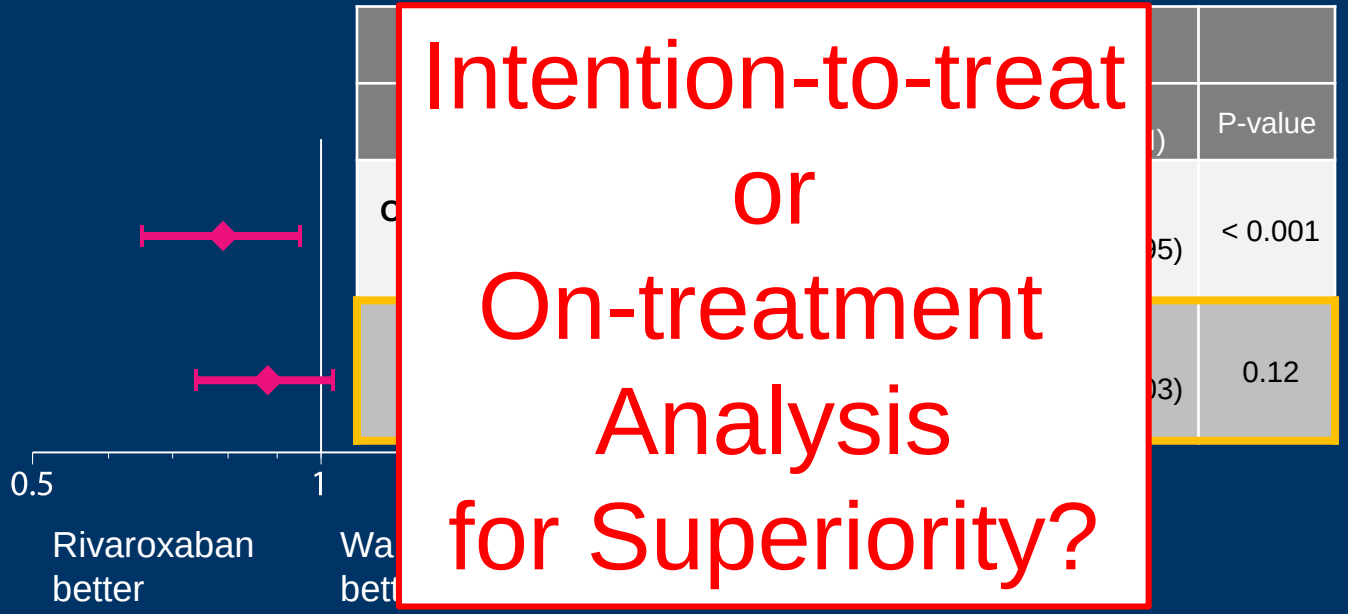
Primary Efficacy Outcome
Stroke and non-CNS Embolism



Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Mahaffey; Oral presentation at AHA, 15th November 2010; Patel MR et al. *N Eng J Med* 2011; 365: 883-991

Primary Efficacy Outcome
Stroke and non-CNS Embolism

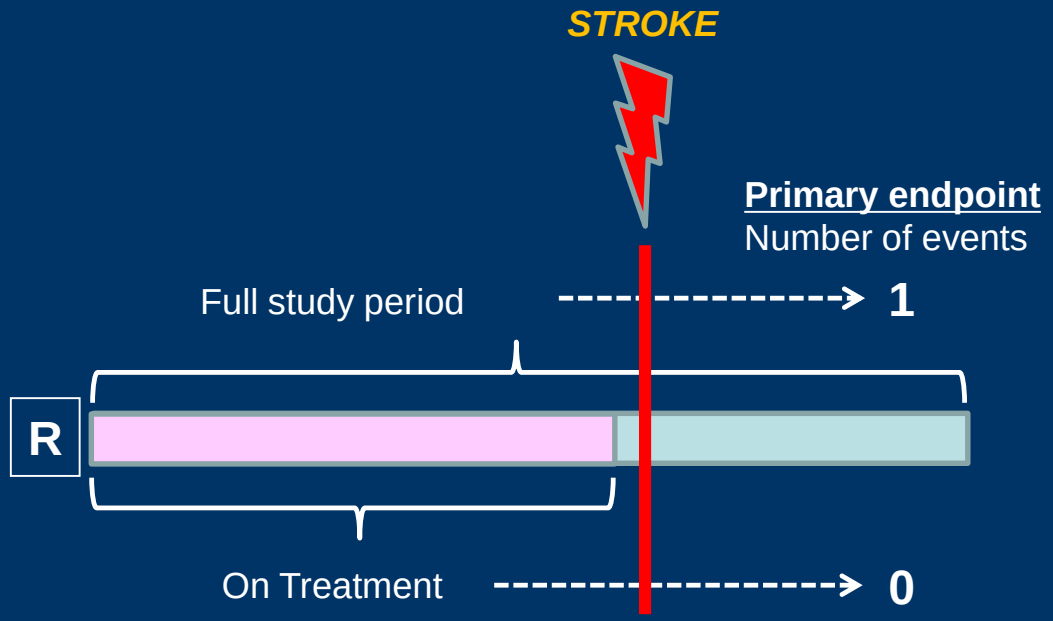


Intention-to-treat or On-treatment Analysis for Superiority?

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

Mahaffey; Oral presentation at AHA, 15th November 2010; Patel MR et al. *N Eng J Med* 2011; 365: 883-991

„Full study period“ vs. „On treatment period“



Non-inferiority: On-treatment analysis

Superiority: Intention-to-treat analysis

Safety: On-treatment analysis

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy (n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)

Warfarin (target INR 2-3)

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Duke Clinical Research Institute

UCR UPPSALA CLINICAL RESEARCH CENTER

Presented at ESC 2011; Granger et al. NEJM 2011;365:981-92

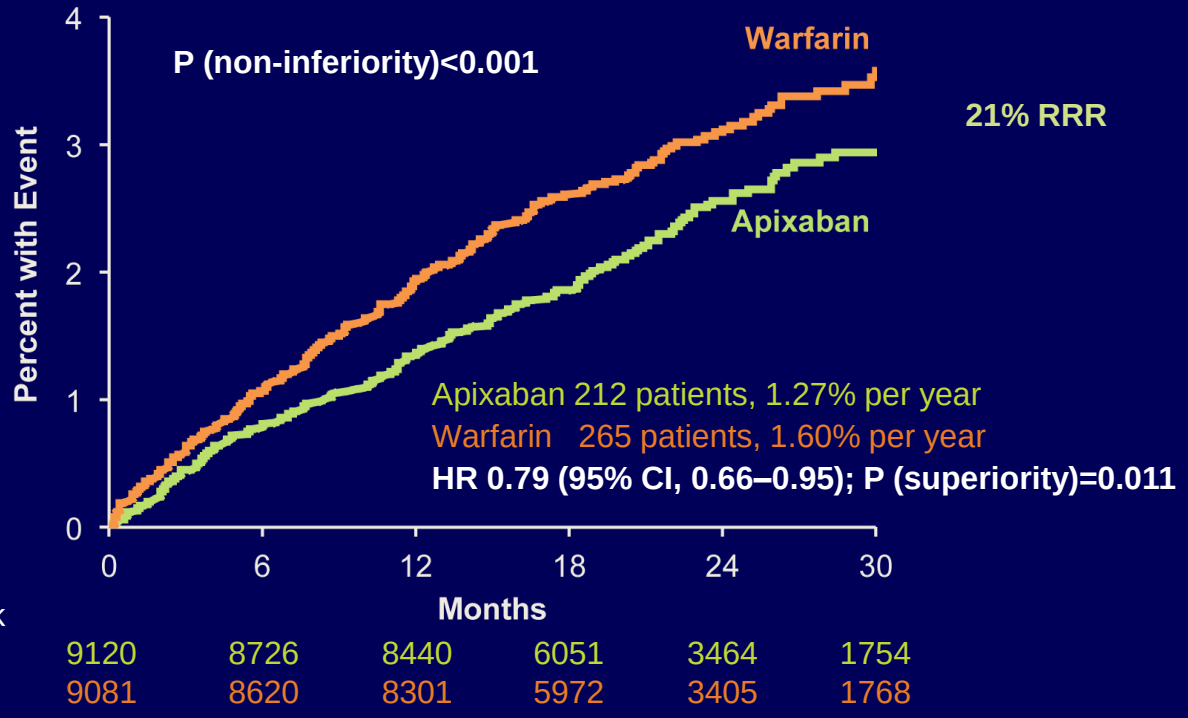
Objectives and Statistics

To control the overall type I error, a pre-specified hierarchical sequential testing was performed.

1. The primary outcome (stroke or systemic embolism) for non-inferiority (upper limit of 95% CI < 1.38 and upper limit of 99% CI < 1.44)
2. If met, then the primary outcome was tested for superiority
3. If met, then major bleeding was tested for superiority
4. If met, then all-cause mortality was tested for superiority

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



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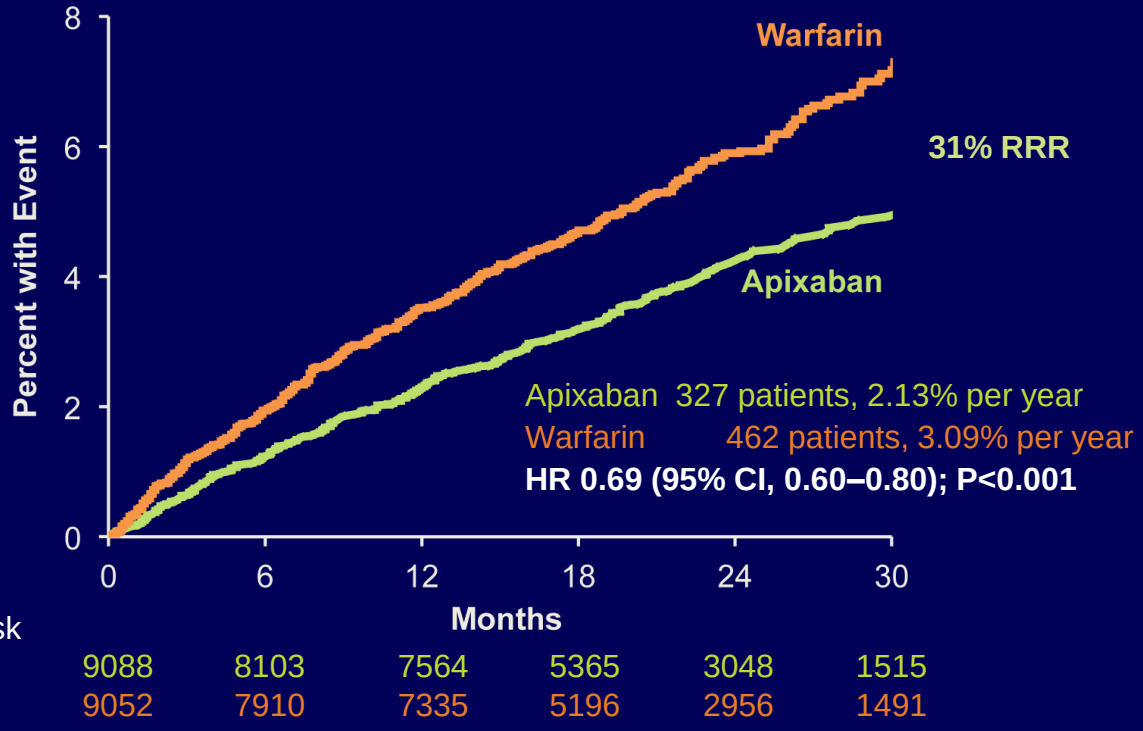
Major Bleeding

ISTH definition



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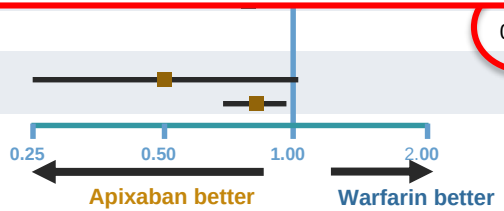
ARISTOTLE: 5 mg BID versus 2.5 mg BID Dose

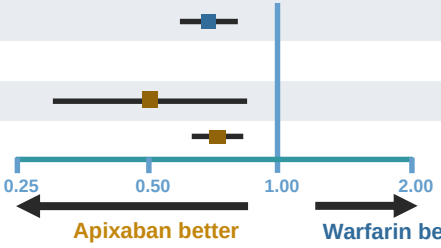
What do we know about the 2.5 mg BID dose?

Pr…					…on
Sub…					
All					
Apixaban dose					0.22
2.5 mg BID or placebo	831	12 (1.7)	22 (3.3)		
5 mg BID or placebo	17 370	200 (1.3)	243 (1.5)		



Major bleeding (secondary endpoint)

Subgroup	Number of patients	Apixaban	Warfarin	Hazard Ratio (95%-CI)	p for interaction
		Number of events (%/y.)			
All patients	18 140	327 (2.13)	462 (3.09)		
Apixaban dose					0.21
2.5 mg BID or placebo	826	20 (3.3)	37 (6.7)		
5 mg BID or placebo	17 314	307 (2.1)	425 (3.0)		



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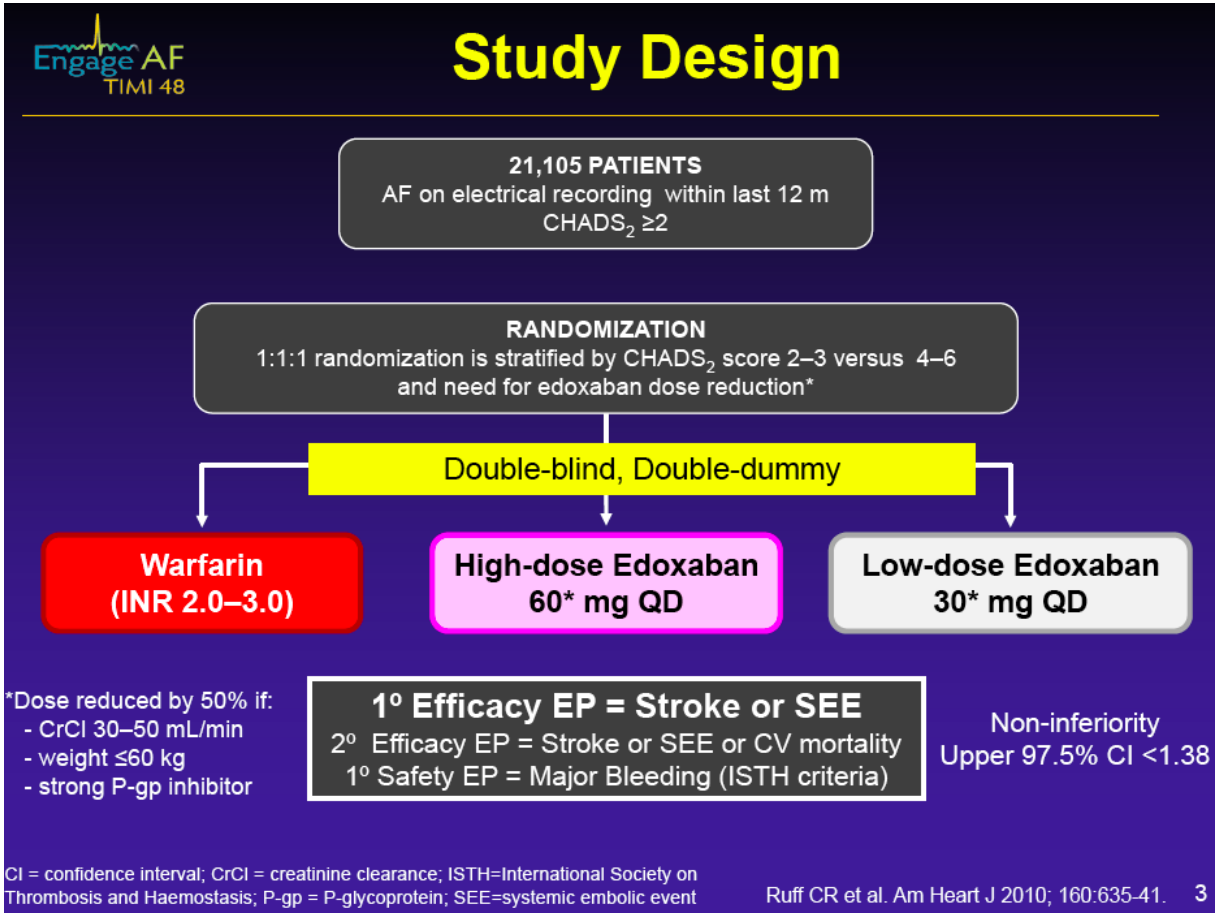
ENGAGE AF – TIMI 48



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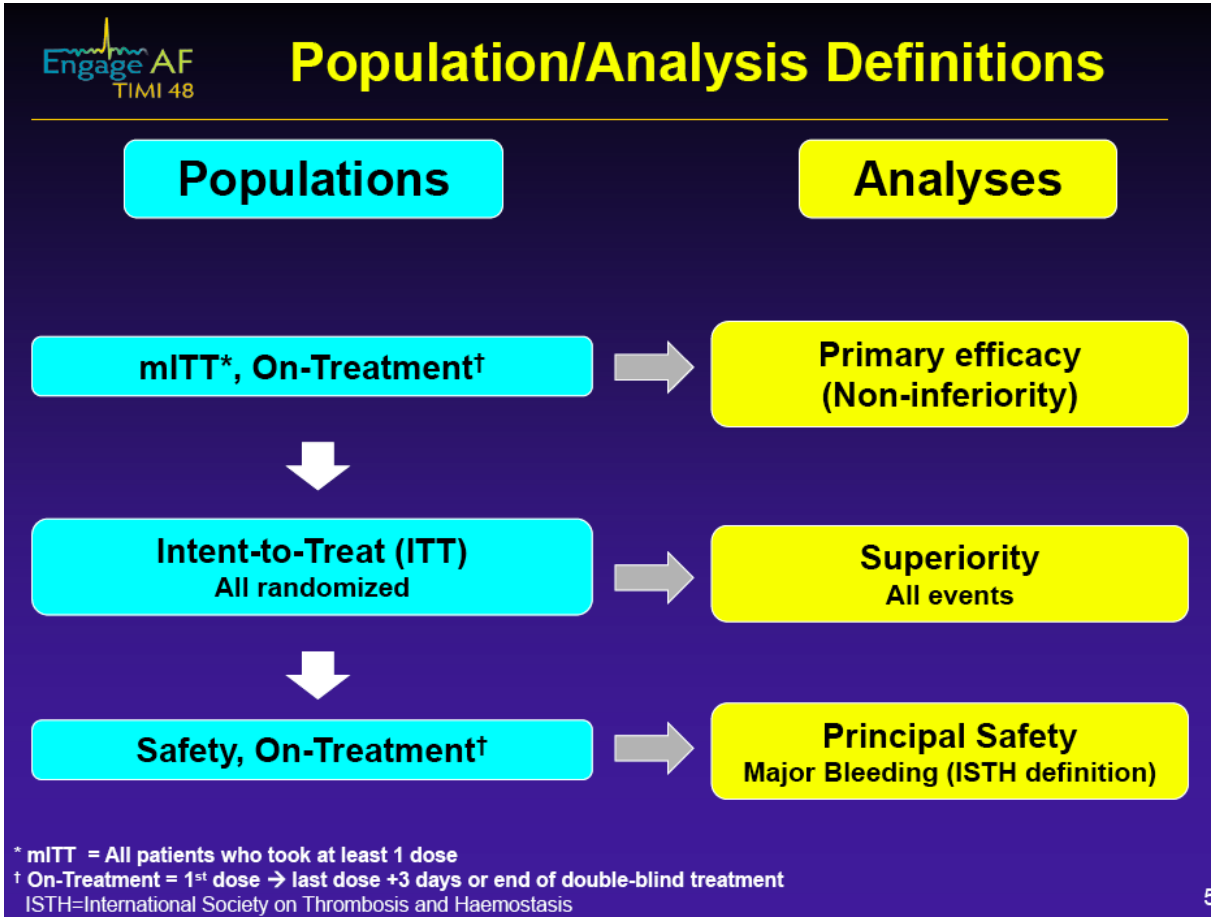

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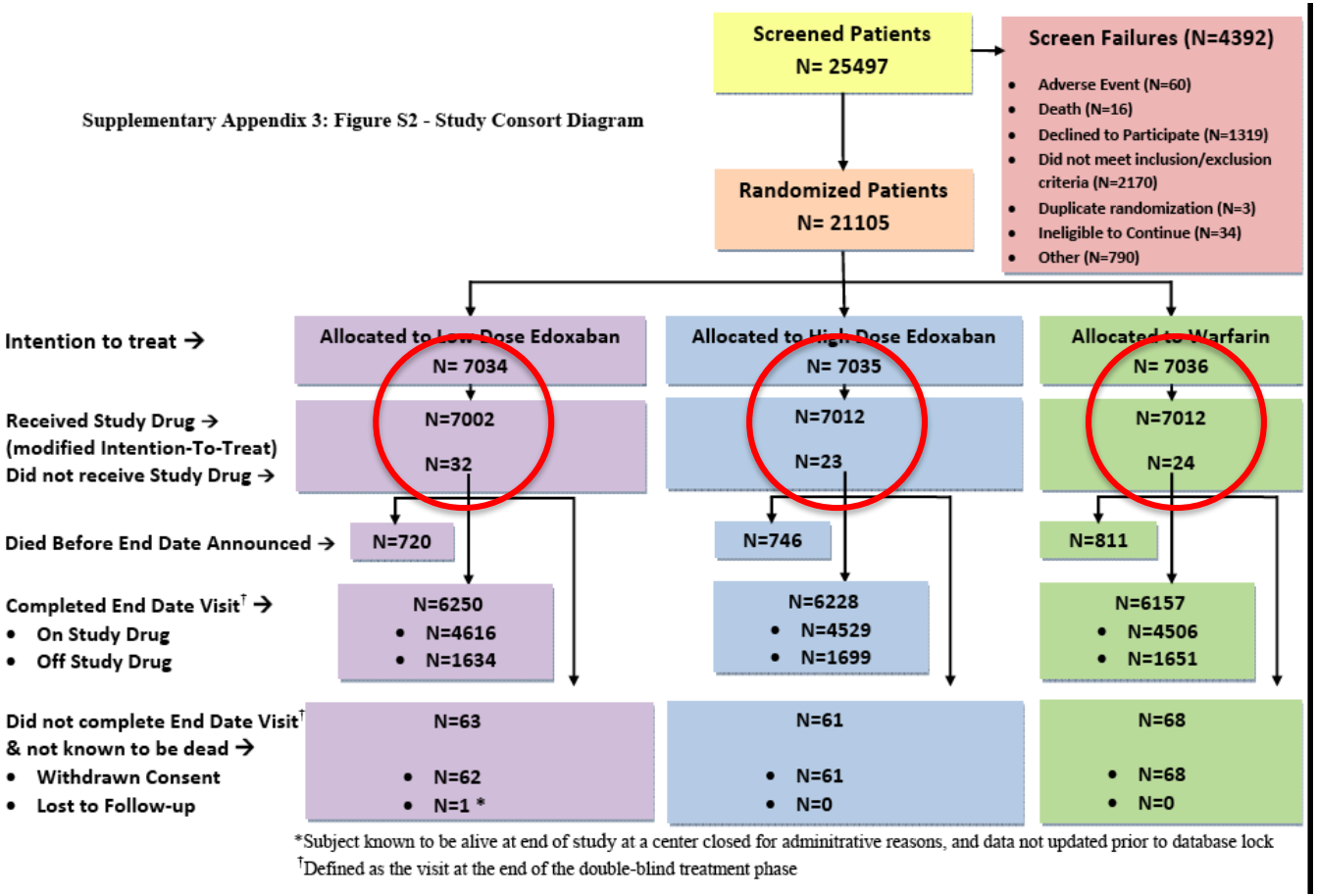

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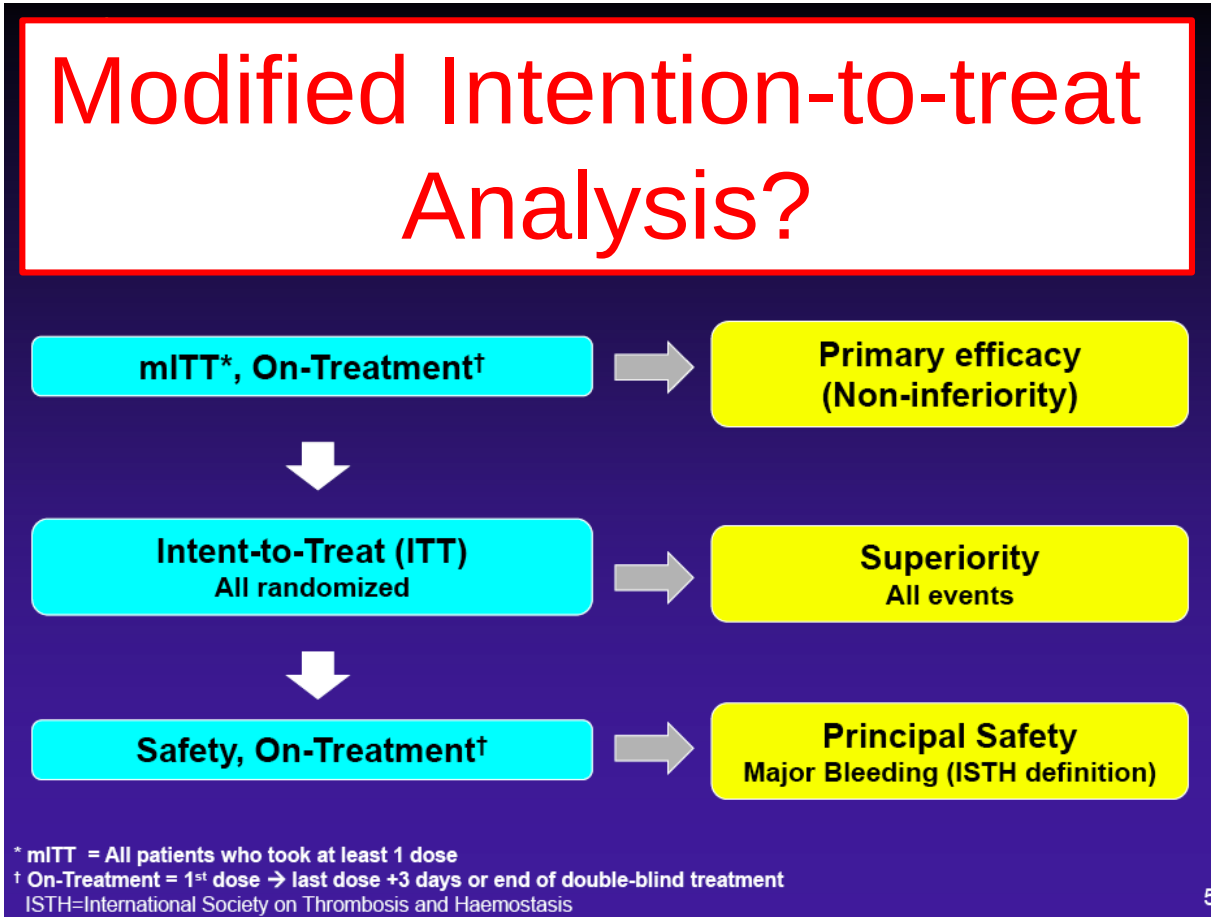

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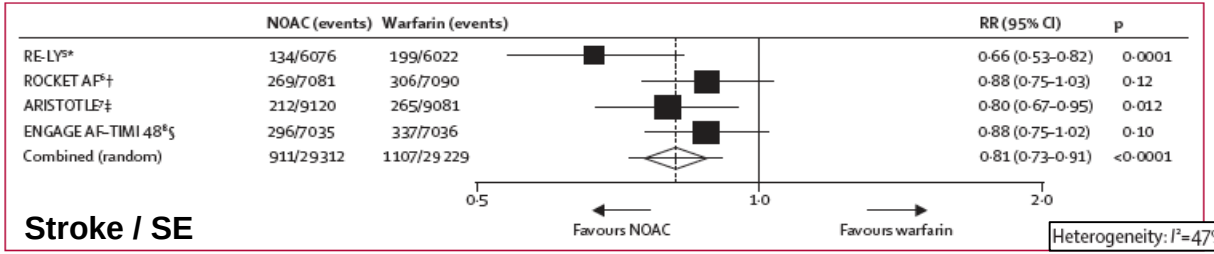
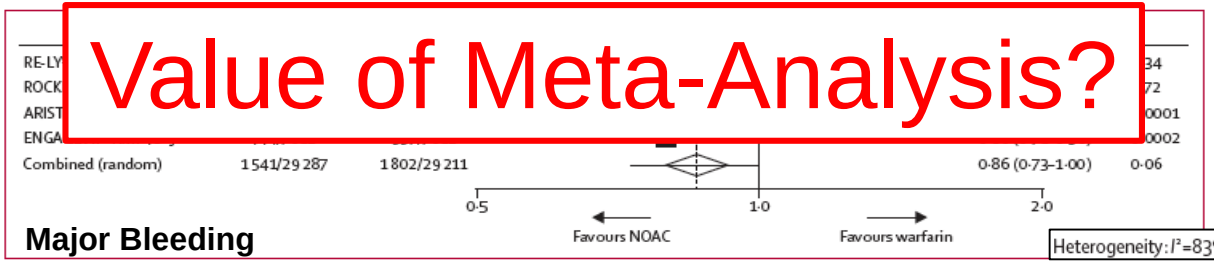
Atrial Fibrillation Trials with NOAC vs Warfarin: Meta-Analysis

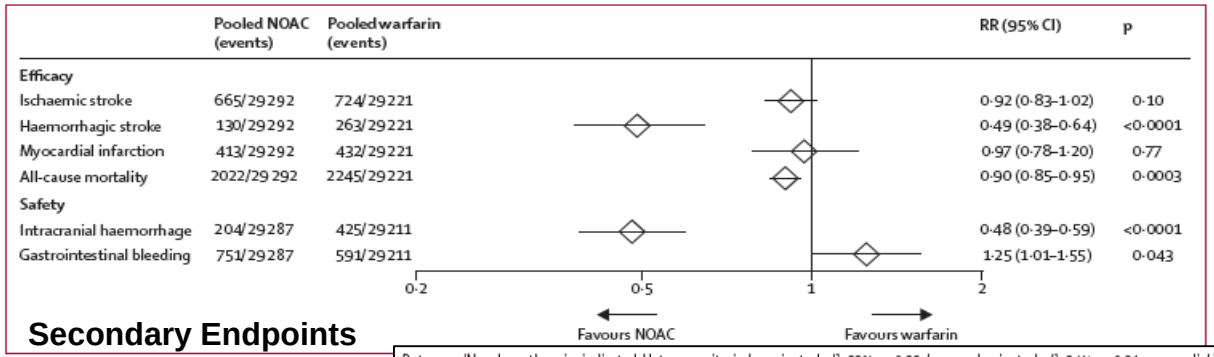


Stroke / SE

Value of Meta-Analysis?



Major Bleeding



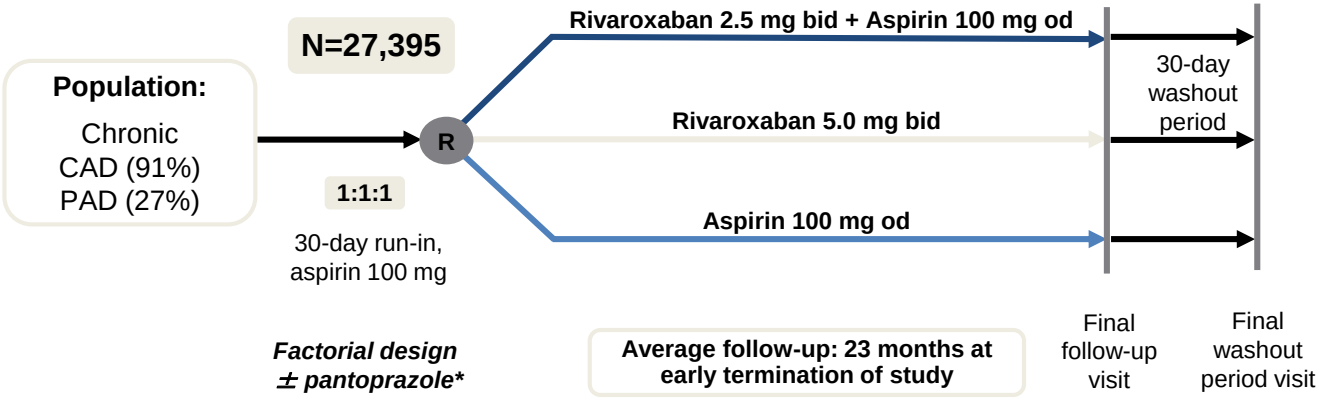
Secondary Endpoints

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant.

Ruff et al., Lancet 2014;383:955-62

COMPASS: Anti-Xa and/or Aspirin in Patients with Chronic CAD and/or PAD

Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD



Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

1. Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118;
2. Bosch J *et al. Can J Cardiol* 2017;33(8):1027–1035

COMPASS

COMPASS: Primary Endpoint and Components

CV Death significantly lower?

Outcomes, n (%)	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
1°: CV death, stroke, or MI	379 (4.1)	496 (5.4)	0.76 (0.66–0.86)	<0.001
CV death	160 (1.7)	203 (2.2)	0.78 (0.64–0.96)	0.02
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44–0.76)	<0.001
MI	178 (1.9)	205 (2.2)	0.86 (0.70–1.05)	0.14

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

COMPASS: Secondary Endpoints

Mortality significantly lower?

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg	
			HR (95% CI)	*p*-value
CHD death, ischaemic stroke, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63–0.83)	<0.001
CV death, ischaemic stroke, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65–0.85)	<0.001
Mortality (all-cause)	313 (3.4%)	378 (4.1%)	0.82 (0.71–0.96)	0.01 §

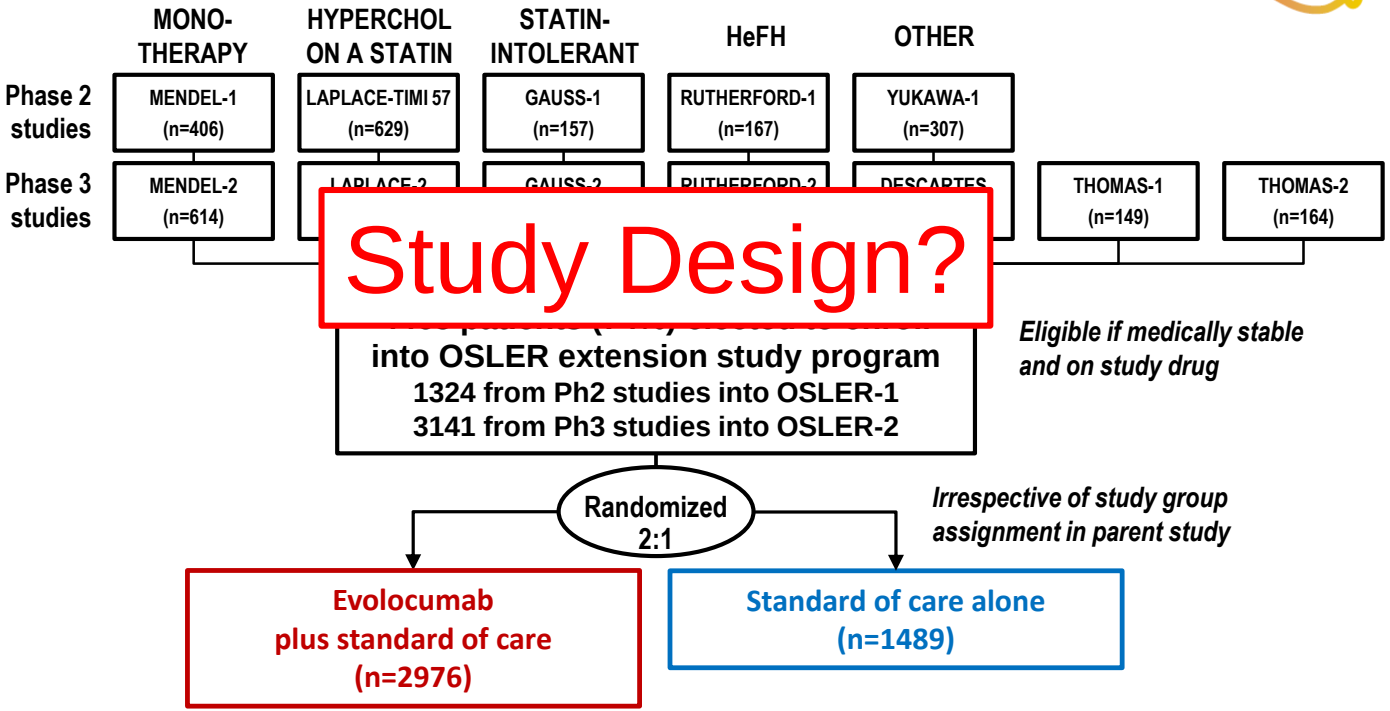
§ The threshold P value using the Hochberg procedure for each of the above comparisons was 0.0025

CHD coronary heart disease death: death due to acute MI, sudden death, or CV procedure

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

OSLER Program



IQR = Interquartile range;
HeFH = Heterozygous familial hypercholesterolemia;
Hyperchol = Hypercholesterolemia

Median follow-up of 11.1 months (IQR 11.0-12.8)
7% discontinued evolocumab early
96% completed follow-up

Data from the two trials (OSLER-1, OSLER-2) were combined

Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

OSLER: Methods

- Evolocumab
  - Open-label randomized, controlled study; subcutaneous injections
  - Dosed 420 mg QM (OSLER-1); either 140 mg Q2W or 420 mg QM on the basis of patient choice (OSLER-2)
- **Primary Endpoints**:
  - Incidence of adverse events (AE) & tolerability
- **Secondary Endpoints**:
  - Percent change in LDL-C level & other lipid parameters
- CV clinical events (**pre-specified, exploratory outcome**): adjudicated by TIMI Study Group CEC*, blinded to treatment
  - Death
  - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
  - Cerebrovascular: stroke or transient ischemic attack (TIA)
  - Heart failure (HF) requiring hospitalization

Patients had in-person clinic visits on day 1 and then quarterly at weeks 12, 24, 36 and 48.

*Thrombolysis in Myocardial Infarction (TIMI) Study Group Clinical Events Committee (CEC)

Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

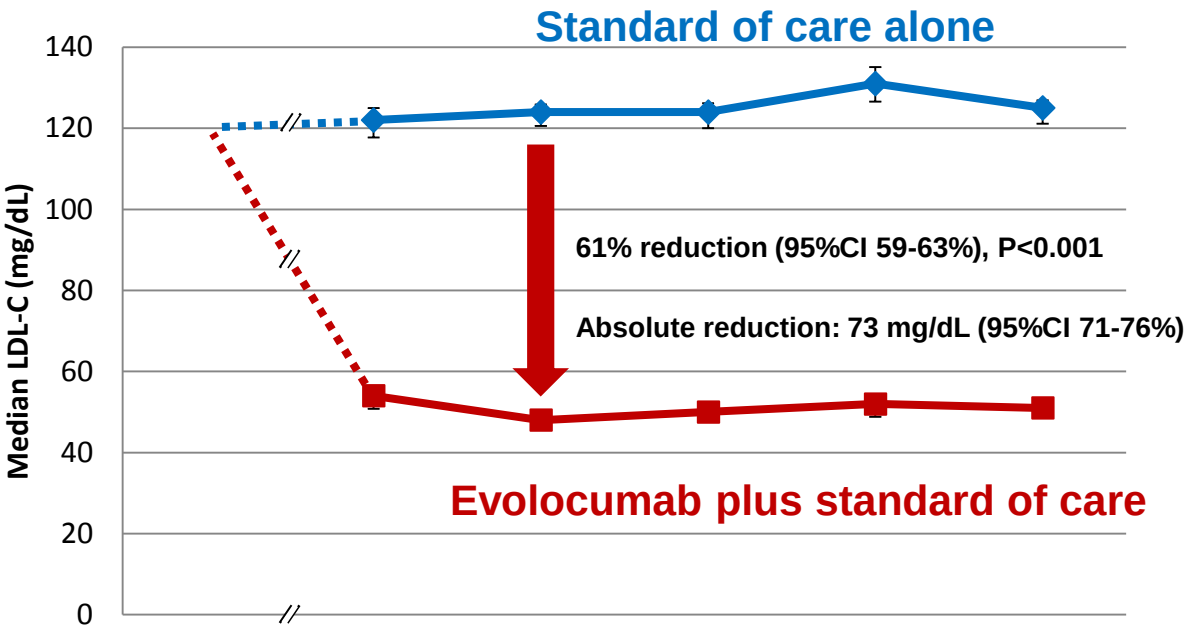
OSLER: Safety

	Evolocumab + Standard of Care (N=2976)	Standard of Care alone (N=1489)
Adverse events	**no. (%)**	
Any	2060 (69.2)	965 (64.8)
Serious	222 (7.5)	111 (7.5)
Leading to discontinuation of evolocumab	71 (2.4)	n/a
Injection-site reactions	129 (4.3)	n/a
Muscle-related	190 (6.4)	90 (6.0)
Neurocognitive*	27 (0.9)	4 (0.3)
Other		
Arthralgia	137 (4.6)	48 (3.2)
Headache	106 (3.6)	32 (2.1)
Limb pain	99 (3.3)	32 (2.1)
Fatigue	83 (2.8)	15 (1.0)
Laboratory results	**no. (%)**	
ALT or AST >3×ULN	31 (1.0)	18 (1.2)
Creatine kinase >5×ULN	17 (0.6)	17 (1.1)

**Neurocognitive events were delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.*

Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

OSLER: LDL Cholesterol

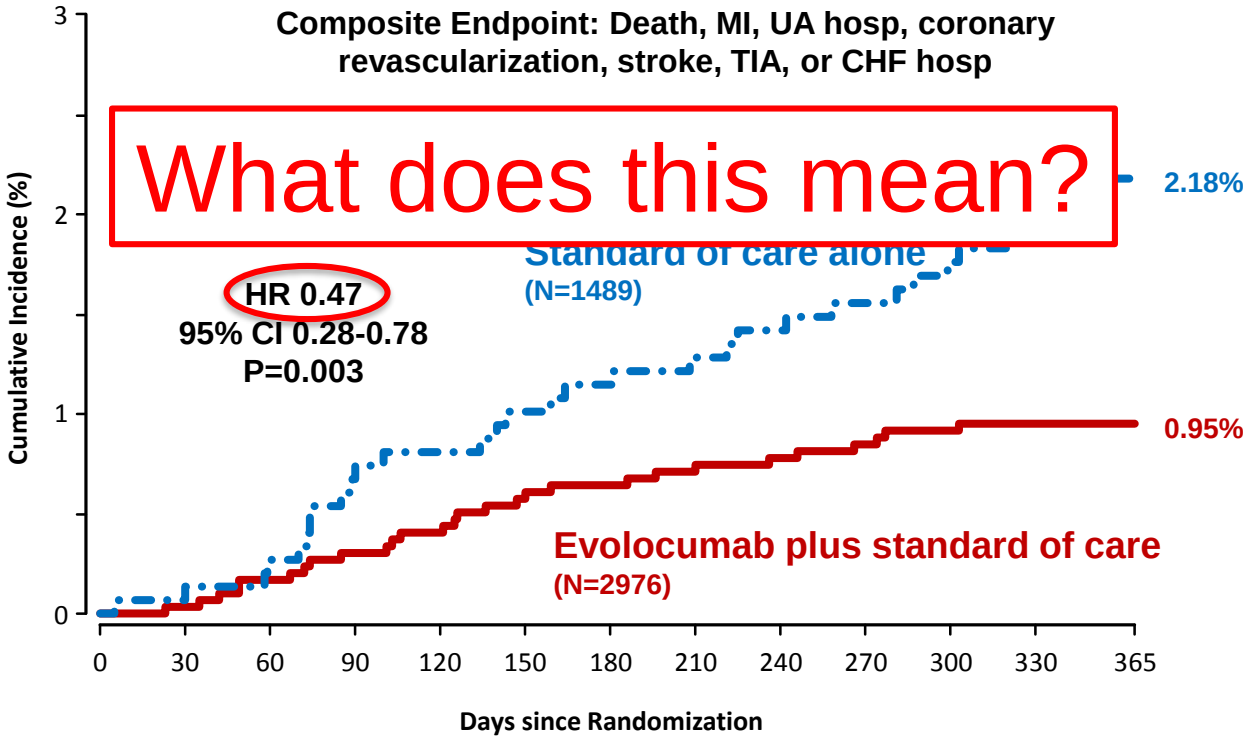


	4 weeks	12 weeks	24 weeks	36 weeks	48 weeks
Abs. reduction (mg/dL)	60.4	73.4	70.4	72.7	70.5
Abs. reduction (mmol/L)	1.56	1.90	1.82	1.88	1.82

The dashed line indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER.

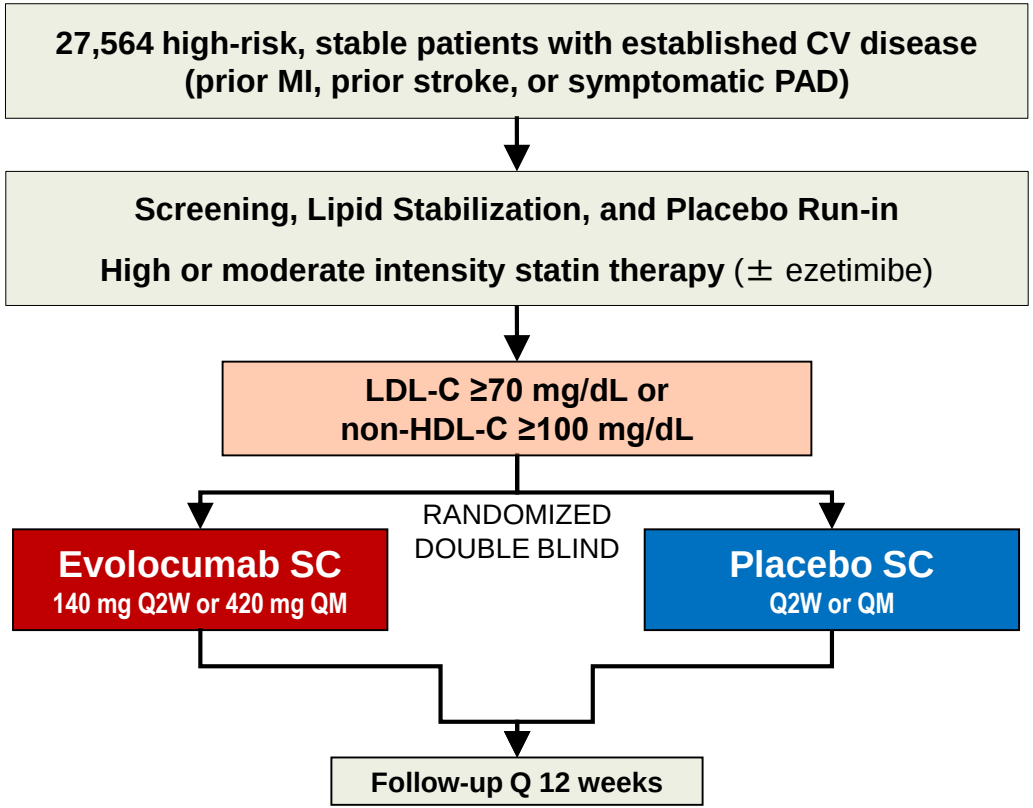
Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

OSLER: Cardiovascular Outcomes



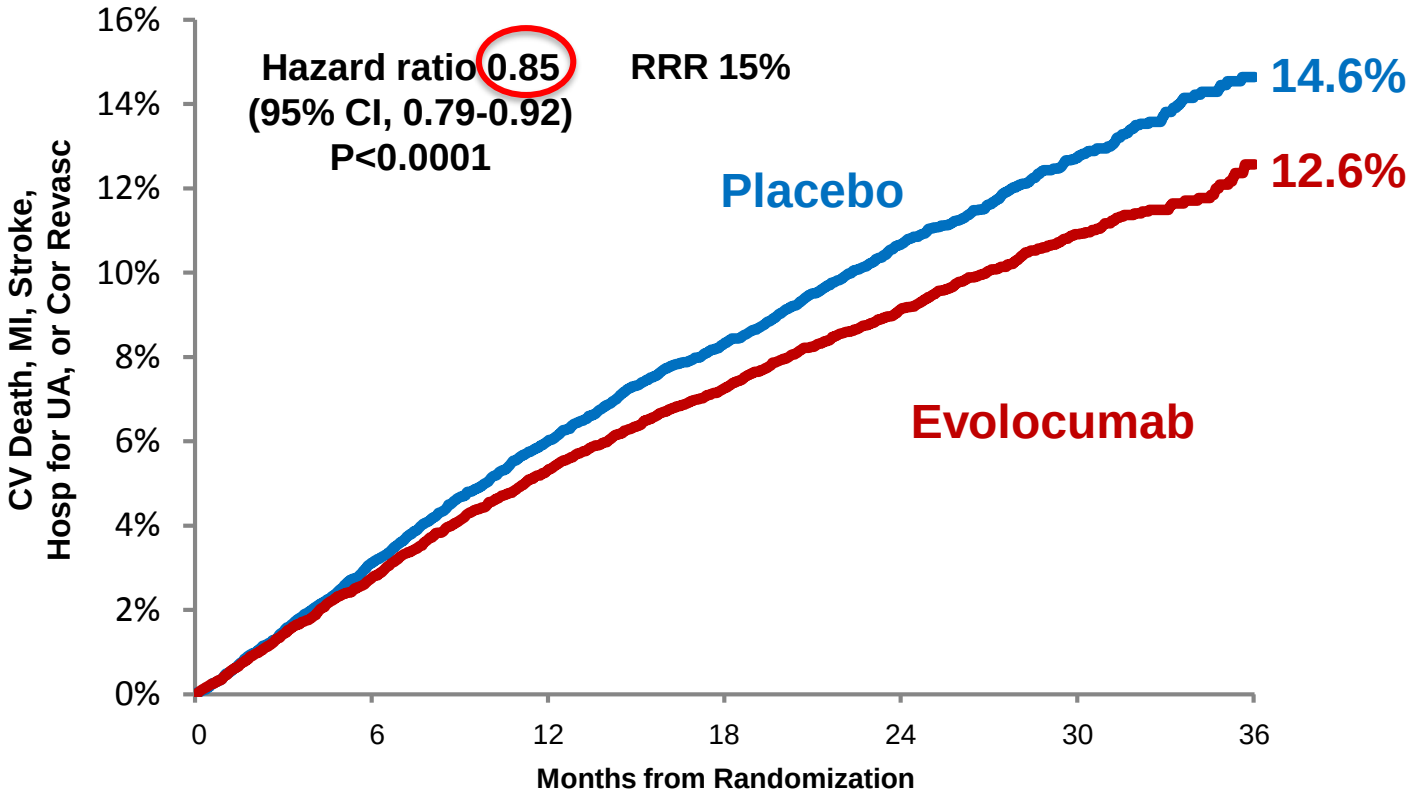
Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

FOURIER: Trial Design



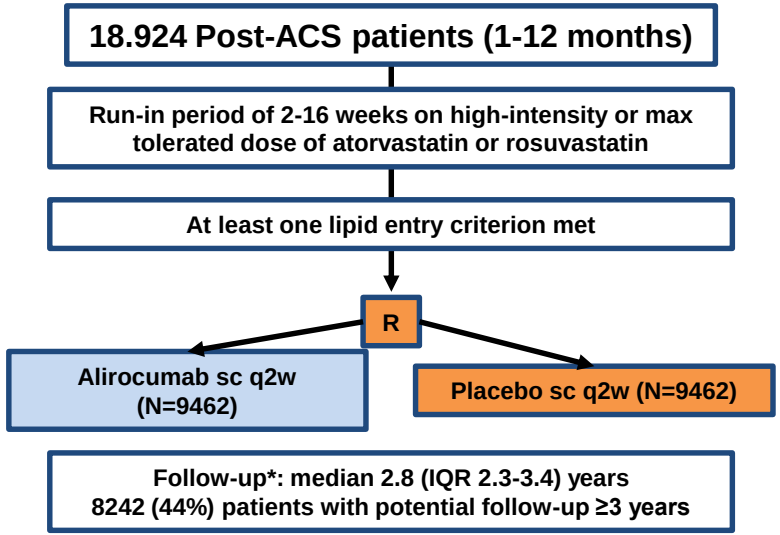
Sabatine MS et al. Am Heart J 2016;173:94-101

FOURIER: Primary Endpoint



Presented at ACC 2017, Washington, USA; Sabatine et al., N Engl J Med 2017;376:1713-1722

ODYSSEY OUTCOMES: Trial Design



Premature treatment discontinuation	1343 (14.2%)	1496 (15.8%)
Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)	730 (7.7%)	Not applicable
Patients lost to follow-up (vital status)	14	9

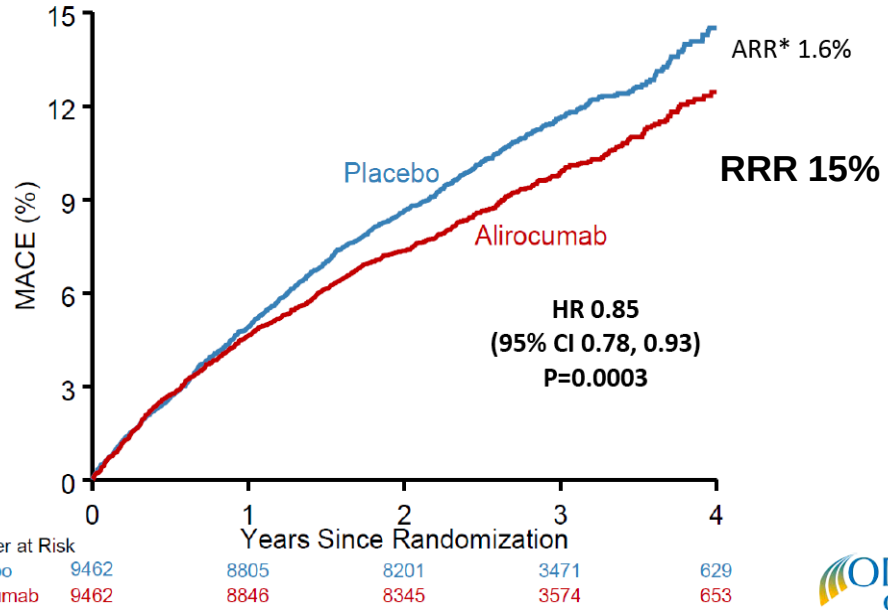
Patient and investigator remained blinded to treatment and lipid levels for the entire duration of the study

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

Presented at ACC 2018, Orlando, FL, USA; Schwartz et al., N Engl J Med. 2018;379:2097-107

ODYSSEY OUTCOMES: Primary Endpoint

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ODYSSEY OUTCOMES

Presented at ACC 2018, Orlando, FL, USA; Schwartz et al., N Engl J Med. 2018;379:2097-107

ODYSSEY OUTCOMES: Secondary Endpoints

Main Secondary Efficacy Endpoints:
Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	1199 (12.7)	1349 (14.3)	0.88 (0.81, 0.95)	0.001
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	205 (2.2)	222 (2.3)	0.92 (0.76, 1.11)	0.38
CV death	240 (2.5)	271 (2.9)	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

Mortality significantly lower?

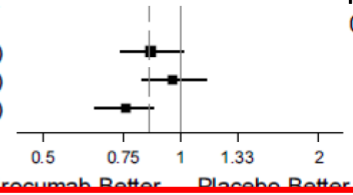
*Nominal P-value

Presented at ACC 2018, Orlando, FL, USA; Schwartz et al., N Engl J Med. 2018;379:2097-107

ODYSSEY OUTCOMES: LDL-C Subgroup Analysis

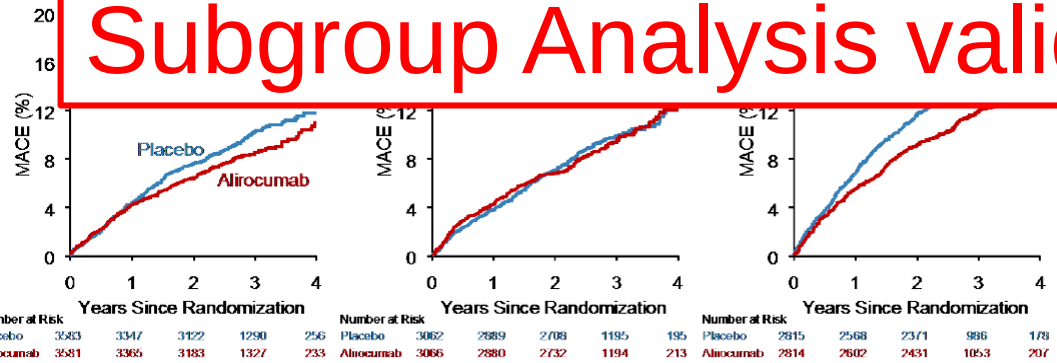
Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Incidence (%) Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction

Subgroup Analysis valid?



ODYSSEY OUTCOMES

Presented at ACC 2018, Orlando, FL, USA; Schwartz et al., N Engl J Med. 2018;379:2097-107

RESPECT Trial

Subject Distribution

Enrolled
N=980

Randomization stratified by site and presence/absence of atrial septal aneurysm

Randomized to device group	Randomized to medical group
N = 499	N = 481
Study device implant attempted N = 464	Medical treatment specified pre-randomization by site neurologist
Post Implant: clopidogrel 1 month and aspirin 6 months. After 6 months, antiplatelet therapy at discretion of site investigator	
TEE with bubble study at 6 months	

Medical treatment specified pre-randomization by site neurologist	
Aspirin only	46.5%
Warfarin only	25.2%
Clopidogrel only	14.0%
Aspirin + dipyridamole	8.1%
Aspirin + clopidogrel[1]	6.2%

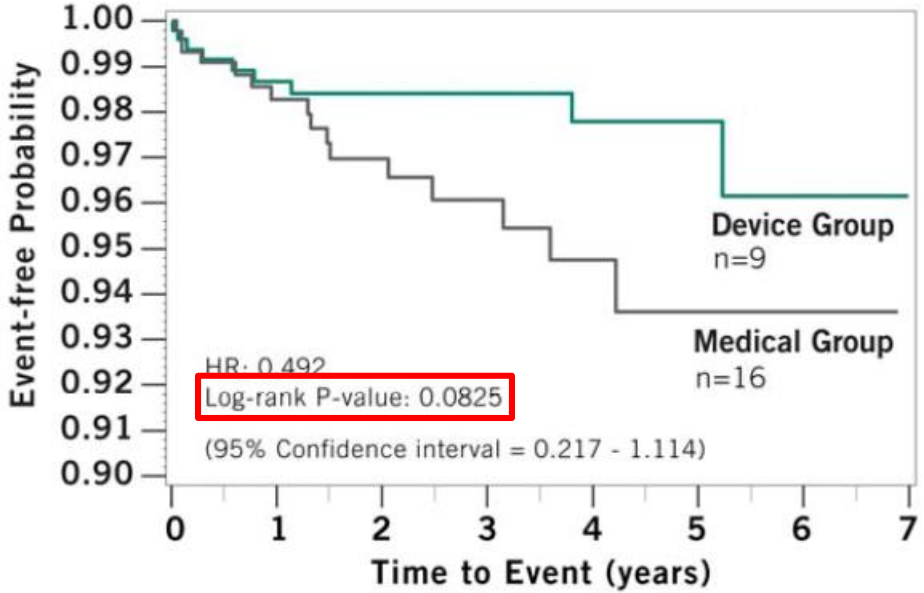
1. Aspirin + clopidogrel was removed from the protocol in 2006 based on changes to the AHA/ASA treatment guidelines

Carroll et al., N Engl J Med 2013;368:1092-100

RESPECT Trial

Primary Endpoint Analysis – ITT Cohort

50.8% risk reduction of stroke in favor of device



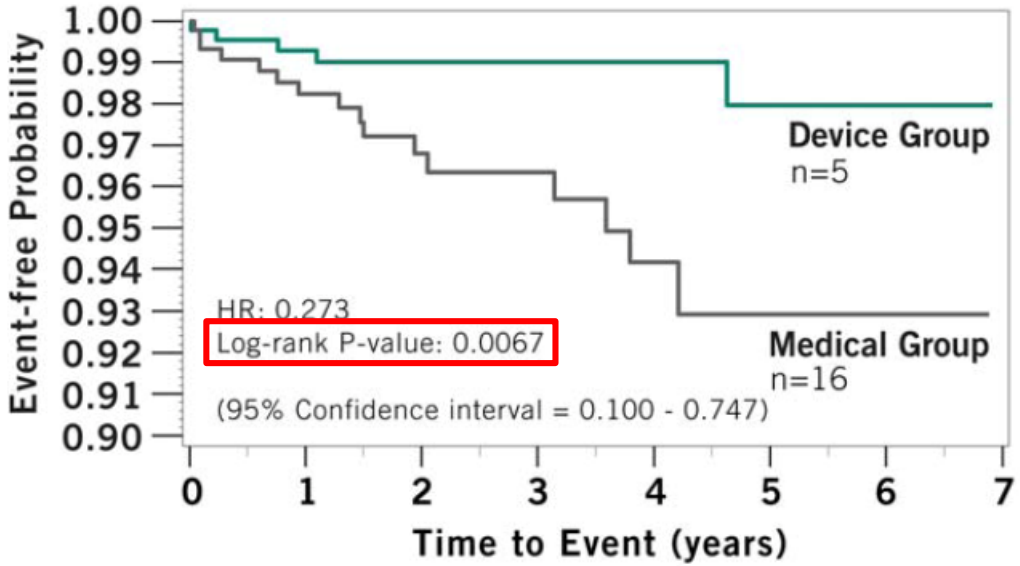
- **3/9** device group patients did not have a device at time of endpoint stroke

Cox model used for analysis

Carroll et al., N Engl J Med 2013;368:1092-100

RESPECT Trial

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device



- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment

Cox model used for analysis

Carroll et al., N Engl J Med 2013;368:1092-100

RESPECT Trial

Totality of Evidence and NNT

46.6%-72.7% risk reduction of stroke in favor of device

Totality of Evidence

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

N Engl J Med 2017; 377:1022-1032 | September 14, 2017 | DOI: 10.1056/NEJMoa1610057

CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

2 Year	70.4	1.60%	3.02%
5 Year	23.9	2.21%	6.40%

P-values: ITT Raw Count is calculated using Fisher's Exact test; all other P-values are calculated using log-rank test
The NNT is the average number of subjects that need to be treated with the AMPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates
Calculated using the Kaplan-Meier estimated event rates for each treatment group

Carroll et al., N Engl J Med 2013;368:1092-100

PFO Closure vs. Medical Therapy: Meta-Analysis of Randomized Controlled Trials

Pineda et al., Cath Cardiovasc Interv 2013; DOI: 10.1002/ccd.25122

Thank you for your attention!

ESC
Working Group
Cardiovascular
Pharmacotherapy